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A pragmatic approach based on current guidelines and point-of-care platelet function testing

Antiplatelet therapy before cardiac surgery

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Summary

Patients under double antiplatelet therapy (DAPT) waiting for cardiac surgery need careful multidisciplinary evaluation by the heart team. The decisions on if and when to stop oral DAPT and if, how and for how long to proceed to a bridge therapy, have to be made on an individual basis taking into consideration the clinical urgency, coronary status, type and anatomical localisation of already implanted stents and platelet function. This individualised approach is also encouraged by the newer guidelines. Point-of-care platelet function analysis is now available and used quite widely. These tests can, therefore, be integrated into simple algorithms and help to guide decisions for perioperative management of DAPT in cardiac surgery settings. The difficulties are mostly not in the function tests, but rather in the preanalytics and interpretation.

New compounds (e.g., cangrelor) offering rapid reversibility with intravenous administration could in the future further simplify the difficult management of these patients.

Key words: cardiac surgery, antiplatelet therapy

out a stent already implanted [4]. These patients evoke a decisional challenge on many levels because of the delicate balance between effective antiplatelet treatment and risk for major bleeding: choice of the right platelet inhibitory drug, timing of surgery, diagnostic and therapeutic strategy before, during and after CABG. There are some published data confirming the high bleeding rate under double antiplatelet therapy (DAPT) [5, 6]. There is, however, a lack of prospective, randomised clinical trials testing and revealing the best strategy in this regard.

The clinical significance of this issue urged the various scientific societies and associations involved to issue guidelines on how to deal with DAPT and the need of CABG based on best available evidence and clinical knowledge.

The aim of this review is to summarise these guidelines and their recommendations according to a generally accepted methodology [7] and to suggest a tailored and applicable approach to these difficult clinical decisions.

Introduction

Bleeding complications and perioperative acute coronary events after coronary artery bypass grafting (CABG) are strongly influenced by the management of pre- and postoperative antithrombotic therapy. Haemorrhagic events needing transfusion of blood products increase perioperative morbidity and mortality and compromise the long-term benefits of CABG [1, 2].

In the last decade, antithrombotic therapy has become more effective and reliable, particularly in the catheter laboratory. Indeed, the success of percutaneous transluminal coronary angioplasty (PTCA) in the context of an acute coronary syndrome (ACS) has improved with the availability of new antiplatelet compounds [3].

Approximately 10% of ACS non-ST-elevation myocardial infarction (NSTEMI) patients will require urgent CABG during their acute hospitalisation, with or with-

Overview of antiplatelet agents and their mechanisms of action

Several platelet inhibitory drugs with different mechanisms of action and routes of administration are nowadays available on the market. These treatments are routinely employed to prevent myocardial infarction in cases of ACS or thrombosis after coronary stent implantation. Mechanisms of action, doses and recovery times after withdrawal of the therapy to prevent perioperative bleeding risk during surgery are briefly summarised in figure 1 and table 1.

Review of current guidelines

Back in 2009 the Canadian Cardiovascular Society recommended that “all ACS patients should be considered for dual antiplatelet therapy with ASA [acetylsalicylic acid] and clopidogrel at the earliest opportunity, despite the possibility of a need for urgent CABG.

Lecture presented at the congress of the Schweizerische Gesellschaft für Kardiologie (SGK) 2015

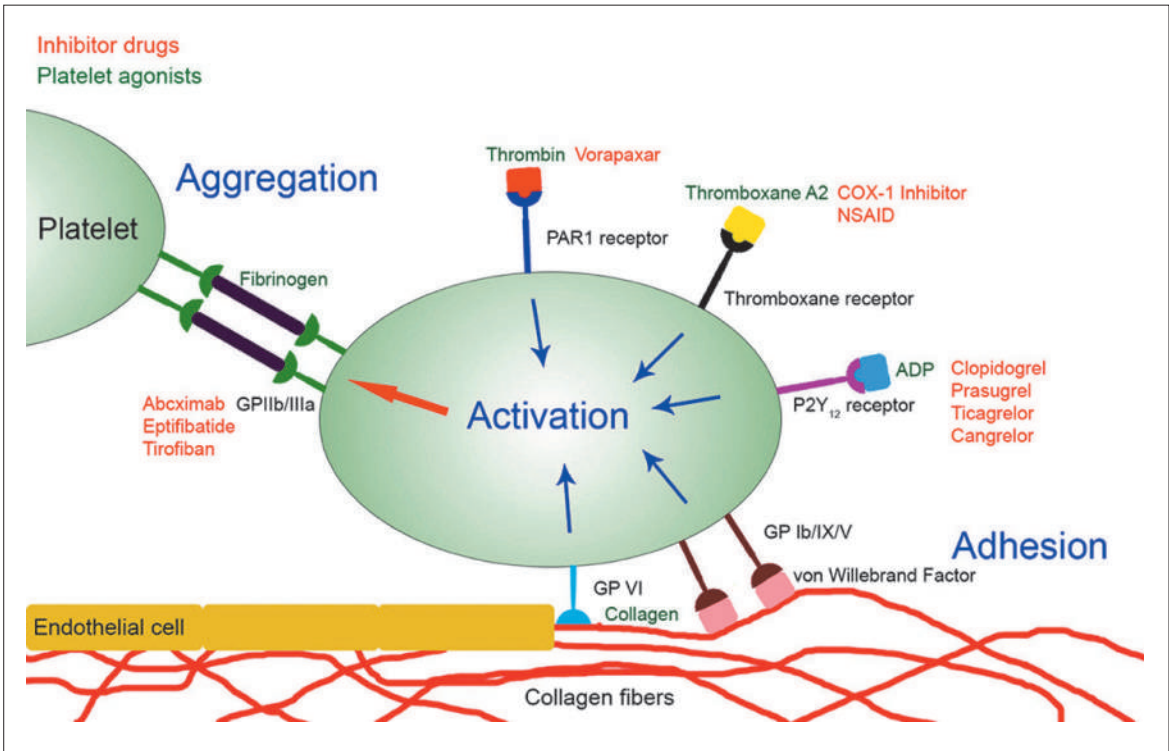


Figure 1: Platelet agonists involved in platelet activation and site of action of inhibitory drugs (modified from [37], with permission of Springer). ADP = adenosine diphosphate; COX = cyclo-oxygenase; GP = glycoprotein; NSAID = nonsteroidal anti-inflammatory drug; PAR = protease-activated receptor

For patients who have received clopidogrel and ASA, and require CABG: those at high risk of an early fatal event (e.g., with refractory ischemia despite optimal medical treatment), and with high-risk coronary anatomy (e.g., severe left main stenosis with severe right coronary artery disease), should be considered for

early surgery without discontinuation of clopidogrel. In patients with a high bleeding risk (e.g., previous surgery, complex surgery) who are also at high risk for an ischemic event, consideration should be given to discontinuing clopidogrel for three to five days before surgery. Patients at a lower risk for ischemic events

Table 1: Platelet inhibitory drugs – mechanism of action, route of administration, dose recommendations and suggested withdrawal before surgery.

Drug	Antiplatelet mechanism	Platelet inhibition	Administration	Loading dose	Maintenance dose	Withdrawal before surgery
Aspirin	Platelet COX-1 inhibitor	Irreversible	Oral/ intravenous	160–325 mg	75–100 mg a day	–
Clopidogrel	ADP P2X ₁₂ receptor antagonist	Irreversible	Oral	300–600 mg	75 mg a day	5 days
Prasugrel	ADP P2X ₁₂ receptor antagonist	Irreversible	Oral	60 mg	10 mg a day	7 days
Ticagrelor	ADP P2X ₁₂ receptor antagonist	Reversible	Oral	180 mg	90 mg twice a day	5 days
Cangrelor	ADP P2X ₁₂ receptor antagonist	Reversible	Intravenous	30 µg/kg	4 µg/kg/min infusion	1 hour
Abciximab	Fibrinogen receptor (GP IIb/IIIa) antagonist	Reversible	Intravenous	0.25 µg/kg	0.125 µg/kg/min (max. 10 µg/min)	24–48 hour
Eptifibatide	Fibrinogen receptor (GP IIb/IIIa) antagonist	Reversible	Intravenous	180 µg/kg	2 µg/kg/min	4–6 hour
Tirofiban	Fibrinogen receptor (IIb/IIIa) antagonist	Reversible	Intravenous	25 µg/kg	0.15 µg/kg/min	4–6 hour
Vorapaxar	Thrombin receptor (PAR-1) antagonist	Reversible	Oral	–	2.5 mg a day	?

ADP = adenosine diphosphate; COX = cyclo-oxygenase; GP = glycoprotein; PAR = protease-activated receptor

(most patients) should stop clopidogrel five days before surgery. The risk of major bleeding in patients undergoing CABG within five days of treatment with clopidogrel and ASA can be minimized by applying multiple strategies before and during surgery" [8]. Besides the differentiated management of antiplatelet therapy, which will be discussed in this paper, surgical strategies aiming to minimise bleeding should also be applied. Avoiding extracorporeal circulation (ECC) could be one of those. Should complete surgical revascularisation be technically difficult in an "off pump" scenario, a culprit-centered surgical approach completed by PTCA – during the same procedure or (preferably) deferred – should be discussed and planned with the interventional cardiologists (hybrid revascularisation). In the case of an "on pump" procedure, coated ECC circuits permit the use of less heparin and can have a positive impact on blood activation. This can reduce the amount of shed blood and activation of fibrinolysis during surgery [9, 10]. The use of antifibrinolytic agents such as tranexamic acid can also reduce intra- and postoperative fibrinolysis and reduce overall bleeding [11, 12].

The Society of Thoracic Surgeons, in a 2012 guideline update on use of antiplatelet drugs in patients having cardiac and noncardiac operations, suggested that aspirin could or should be discontinued before elective CABG in patients without ACS (Class IIa, Level B). The same guideline [13] stated: "Discontinuation of P2Y₁₂ inhibitors for a few days before cardiovascular operations is recommended to reduce bleeding and blood transfusion, especially in high-risk patients. Stopping antiplatelet drugs before operation is associated with reduced bleeding, blood transfusion, and reoperation but not with increased postoperative death, myocardial infarction, or stroke. The interval between discontinuation of antiplatelet drugs and operation is uncertain and depends on multiple factors mostly related to patient drug responsiveness and thrombotic risk. This recommendation was given a Class I, Level B level of evidence" [13]. There was no recommendation on the exact number of days before surgery to discontinue DAPT, since "the interval between discontinuation of anti-platelet drugs and operation is uncertain and depends on multiple factors mostly related to patient drug responsiveness and thrombotic risk" [13]. However, the same guidelines state that for patients on DAPT who require urgent operation "it is reasonable to make decisions about surgical delay based on tests of platelet inhibition rather than arbitrary use of a specified period of surgical delay (Class IIa, Level B)".

In the most recent guidelines issued by the American Heart Association and American College of Cardiology

and developed in collaboration with the Society for Cardiovascular Angiography and Interventions and Society of Thoracic Surgeons [14], a specific section was dedicated to the timing of urgent CABG in patients with NSTEMI type of ACS, depending on the patient's cardiac risks as well as on pharmacokinetic and pharmacodynamic properties of antiplatelet drugs:

Non-enteric-coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG (Class I, Level B). In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery (Class I, Level B) and prasugrel for at least 7 days before surgery (Class I, Level C). In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding (Class I, Level B). In patients referred for CABG, short-acting intravenous glycoprotein (GP) IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion (Class I, Level B). In patients referred for urgent CABG, it may be reasonable to perform surgery less than 5 days after clopidogrel or ticagrelor has been discontinued and less than 7 days after prasugrel has been discontinued (Class IIb, Level C).

The recent guidelines are completed by the "Expert Position Paper" of the European Society of Cardiology published in 2014 [15]: there is a Class I (Level C) recommendation regarding low-dose ASA: "low-dose ASA (75–160 mg) should be maintained in patients undergoing CABG surgery." However, and similar to the STS guidelines, for patients with increased bleeding risk and for those who refuse blood transfusion, withdrawal of ASA 3–5 days before surgery is recommended, based on individualised assessment of ischaemic and bleeding risks [15]. Regarding the use of P2Y₁₂ inhibitors in patients needing CABG, it is recommended to postpone surgery for 5 days after interruption of ticagrelor or clopidogrel, and 7 days for prasugrel, unless the patient is at high risk of ischaemic events (Class I, Level B) [15].

The same position paper expresses important additional recommendations:

Heart team assessment and platelet function monitoring

- 1 The risks of bleeding and thrombosis, and decision-making regarding DAPT and timing of surgery should be assessed by the heart team prior to CABG surgery (Class I, Level C).
- 2 It is reasonable to base timing of surgery on platelet function monitoring rather than arbitrary use of a specified period of delay in patients on DAPT (Class IIa, Level C).

Bridging therapy

- 1 Bridging with cangrelor, if available, is recommended in high-risk patients (Class I, Level B recommendation).
- 2 Bridging with short-acting intravenous GPIIb/IIIa inhibitors may be considered in patients at high risk for ischaemic events (Class IIb, Level C).

Point-of-care platelet function analysis approach: tailoring of decision-making

Several methods for platelet function testing are available nowadays [16–19]. Most of them, as for example light transmission aggregometry, which is still considered the reference method and “golden standard”, must be performed on centrifuged platelet-rich plasma in a laboratory setting. These in-laboratory tests can be complex, time-consuming and require special laboratory training. Point-of-care (POC) tests on whole blood were recently developed. These new analyses can be performed outside a classical laboratory, in a near

patient setting, for example in the operating theatre or in the intensive care unit [20]. Potential advantages of this kind of test could be readily available results, simplified workflow (rapid turnaround time, no transport of sample to laboratory) and targeted management of coagulation disorders. Of this newly available technology, two devices (VerifyNow® and Multiplate®) are the more routinely employed to assess efficacy and intensity of DAPT in cardiac patients.

VerifyNow® (Accumetrics, San Diego, CA, USA) is a fully automated device not requiring any pipetting. A citrated tube containing the blood sample is directly inserted within the mixing chamber of special disposable cartridges. Cartridges contain fibrinogen-coated polystyrene beads and specific platelet activators [arachidonic acid (AA) or adenosine diphosphate (ADP)]. Stimulated platelets activate GPIIb/IIIa receptors on their surface, which bind fibrinogen on the beads. Agglutinated beads and platelets complexes fall out of the solution, which becomes more transparent. Light transmittance through the mixing chamber is continuously measured by the device and directly correlated

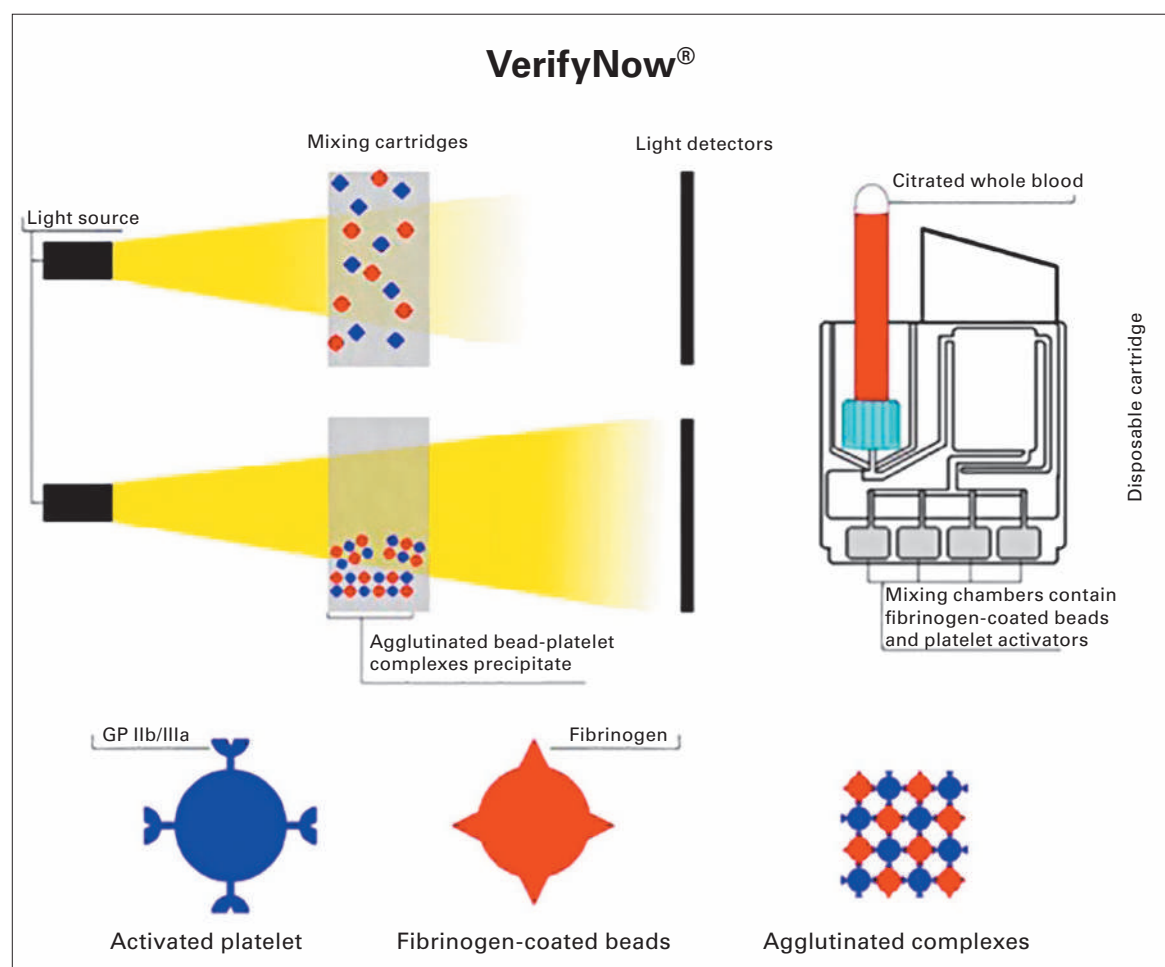


Figure 2: Working mechanism of VerifyNow® system (modified from [37], with permission of Springer).

to the proportion of platelet activation. Direct pharmacological blockade of receptors or decrease of their expression by inhibitor drugs diminishes platelet aggregation and therefore light transmittance (fig. 2). The Multiplate® analyser (Roche Diagnostics, Rotkreuz, Switzerland) is a whole-blood assay that utilises electrical impedance aggregometry to measure platelet function [21]. Impedance aggregometry is based on the principle that platelets are nonthrombogenic in their resting state, but change shape and expose receptors on their surface when activated, allowing them to adhere to vascular injuries and artificial surfaces. The Multiplate® analyser provides a disposable test cuvette containing two independent sensor units, each consisting of two highly conductive metallic wires. A small quantity of whole blood anticoagulated with hirudin is mixed with a saline solution and incubated briefly. A specific platelet activator is then added to the solution (e.g., AA, ADP or thrombin-receptor-activating peptide [TRAP]). Activated platelets adhere to and aggregate on sensor electrodes immersed in blood. This leads to an enhanced resistance between sensor metallic wires,

which is continuously recorded (over a 6-minute period) and expressed as aggregation units (fig. 3).

In conclusion, light transmittance aggregometry (VerifyNow®) and impedance aggregometry (Multiplate®) are two bedside platelet function analysis devices able to measure, in whole blood, specific drug-induced platelet inhibition. Resistance (high on-treatment platelet reactivity) to some antithrombotic therapies (e.g., clopidogrel) or strong inhibition associated with increased risk of bleeding can nowadays be quickly and easily measured in the perioperative setting. It has to be noted, however, that platelet aggregation by itself might be inadequate to assess the bioavailability of an antiplatelet agent [22] and its potential effects on clinically relevant thrombotic or bleeding events.

Discussion

Drug-eluting stents were introduced more than 10 years ago with a main aim to counteract the significant rate of restenosis occurring with bare metal stents. The antiproliferative properties of the eluted drugs were

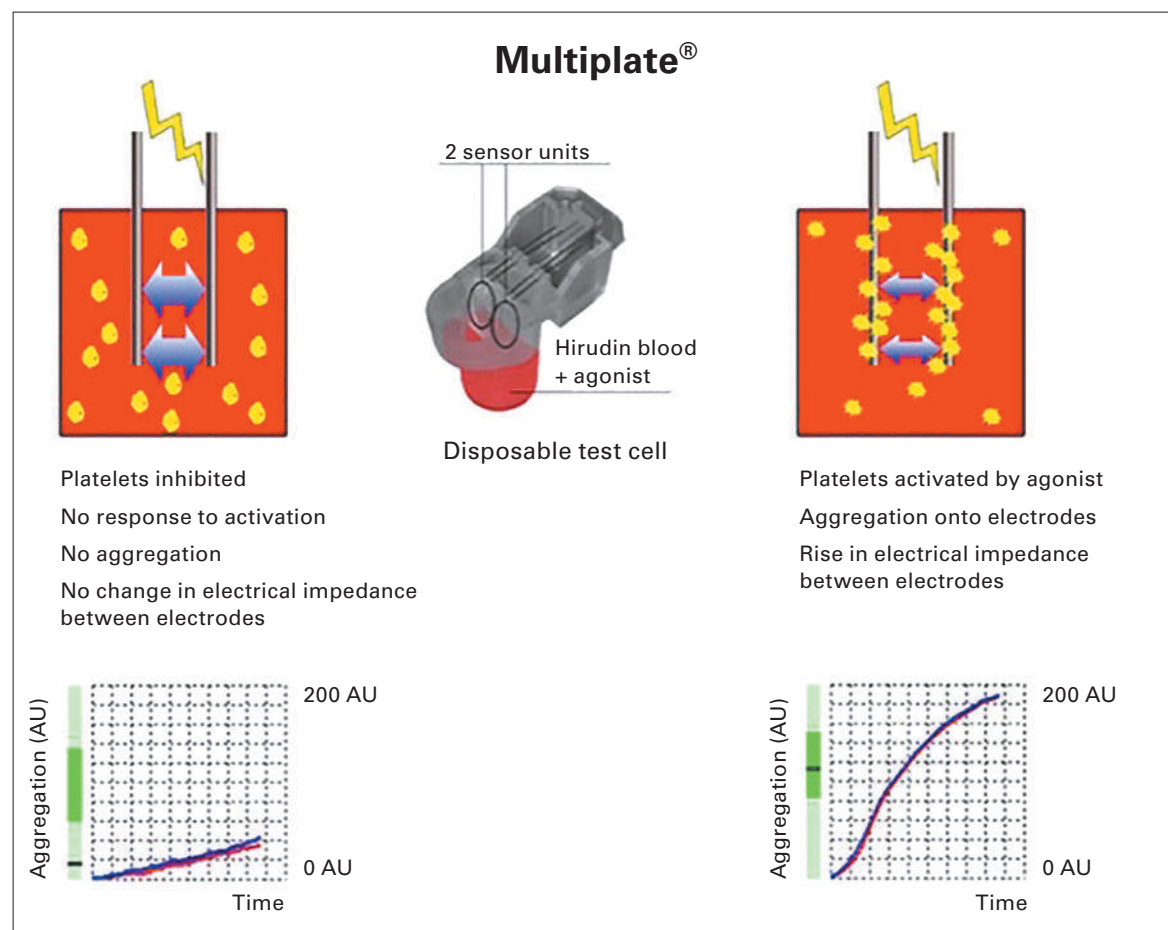


Figure 3: Working mechanism of impedance aggregometry Multiplate® (modified from [37], with permission of Springer).

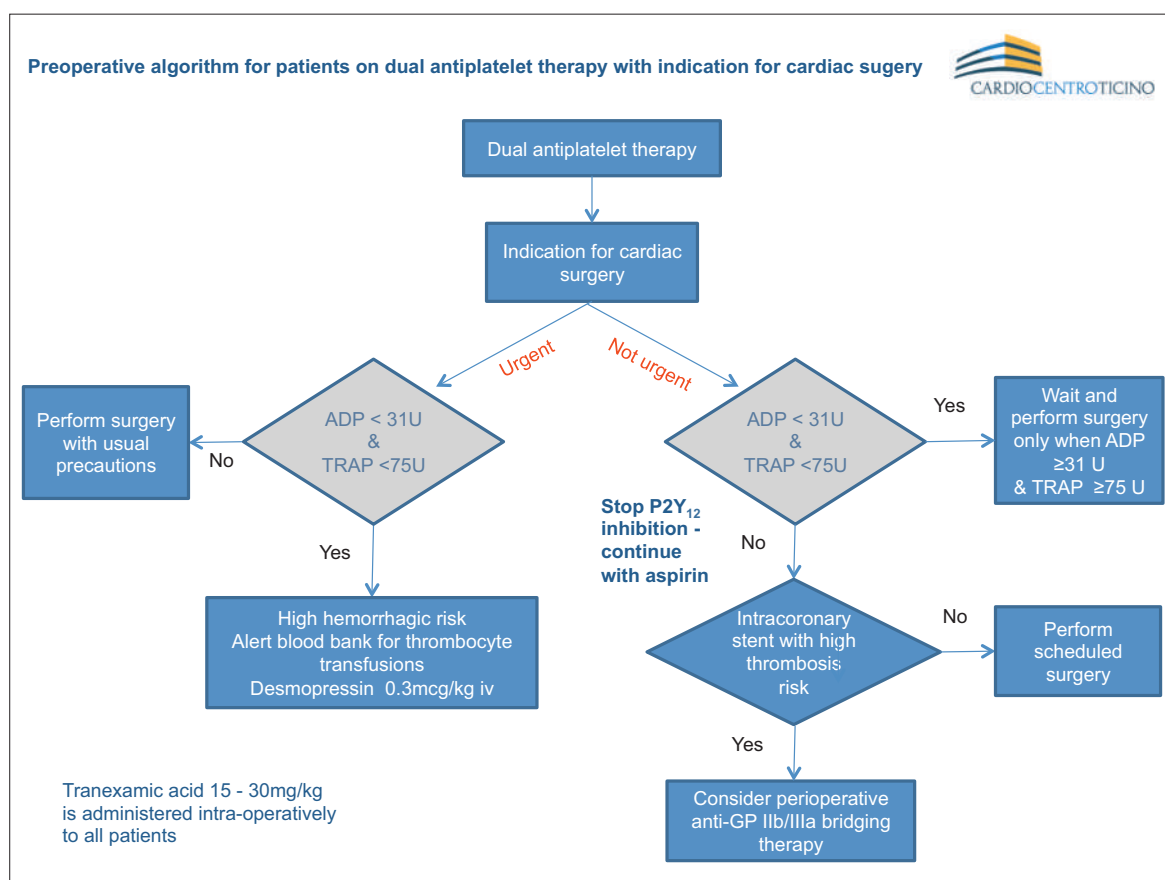


Figure 4: Preoperative decisional flow-chart as used currently at the Cardiocentro Ticino.

ADP = adenosine diphosphate; TRAP = thrombin receptor activating peptide

proved to be effective against the proliferation of smooth muscle cells. At the same time, however, they inhibited and delayed new endothelialisation, resulting in longer exposure of thrombogenic material to the bloodstream [23]. The need to increase the intensity and specificity, as well as to prolong the duration, of DAPT was the direct consequence and the right choice to protect patients from deleterious acute stent thrombosis [24]. There are still more aspects of mid-term DAPT to be clarified for every specific stent subcategory, but the tendency seems, however, to be towards longer periods of DAPT therapy.

In the acute setting, especially NSTEMI-type of ACS, and with special regard to patients needing urgent (or emergent) CABG surgery, the right strategy is more difficult to standardise. Clinical instability can impose an earlier than foreseen operation, which in turn can cause significant bleeding despite best efforts to treat coagulopathy during and after surgery. Here the individualised concept of the POC measurements can eventually help us with the decision.

In cardiac surgery, especially on pump, bleeding can be associated with multifactorial causes. Preoperative

strong antiplatelet-drug-induced inhibition is an important contributory factor that is correlated with increased postoperative bleeding and platelet transfusion requirement [2, 25–30].

Preoperative platelet function analysis can, therefore, be helpful to assess bleeding risk before cardiac surgery in patients treated with DAPT. A clear cut-off value of platelet function that avoids severe perioperative bleeding has not been identified so far.

Two single-centre retrospective studies using impedance aggregometry (Multiplate®) showed a relationship between intensity of preoperative thienopyridine inhibition of the P2Y₁₂ receptor and severity of perioperative bleeding [26, 31]. In the first study, published in 2011, the primary endpoint was severe postoperative bleeding defined as more than 800 ml chest drain blood loss in the first 12 postoperative hours. A cut-off value for the ADP test at 31 U predicted postoperative severe bleeding quite accurately. In a second retrospective study, published by the same group in 2014 and including a larger cohort of 361 patients, severe bleeding was defined in a more restrictive way using the Universal Definition of Perioperative Bleeding in

adult cardiac surgery (severe bleeding defined as drain fluid loss >1000 ml in the first 12 postoperative hours, or need of surgical re-exploration, or need of >5 units of red blood cells or fresh frozen plasma). In this study the ADP threshold was lower than in the first publication. A threshold of 22 U yielded a negative predictive value for severe postoperative bleeding of 94%. Thrombin platelet activation capacity (via protease-activated receptor stimulation) was also assessed using the thrombin receptor activating peptide (TRAP) test. A TRAP test result of ≥ 75 U was associated with a negative predictive value of 95% for severe postoperative bleeding [31].

POC coagulation assessment was introduced 5 years ago by anaesthesiologists in our centre and since then has been routinely used to check perioperative haemostasis. Impedance aggregometry on whole blood (Multiplate®) was locally chosen by us as platelet function analyzer on the basis of highly correlated results and good agreement with the in-laboratory reference method (light transmission aggregometry on centrifuged platelet-rich plasma [32, 33] despite some conflicting cross-comparisons [34, 35]). Furthermore, Multiplate® showed satisfactory validity in the perioperative cardiosurgical setting [36]. Notwithstanding little widely confirmed scientific evidence, we locally decided to develop a simple individualised decision-making preoperative algorithm based on platelet function for cardiosurgical patients on DAPT. This algorithm is intended to help us to determine the time of surgery

and management of perioperative antiplatelet therapy. Platelet function is assessed in our centre by impedance aggregometry on whole blood (Multiplate®). Our local algorithm (fig. 4) is based on the few published studies presented above. It has to be stressed that this approach is not further validated and needs to be confirmed by appropriate trials or at least registries reporting on bleeding rates, particularly if the operation took place earlier than recommended, based on the POC result. In order to limit as much as possible the risk of bleeding of our surgical patients, we decided to keep in our algorithm the most protective ADP test cut-off of 31 U [26], even after publication of the second study of Ranucci et al. [31]. Simultaneous TRAP testing is also always assessed and a recovery of more than 75 U is mandatory to confirm an adequate response to thrombin-mediated activation of the platelets and to further decrease the risk of severe bleeding.

POC coagulation assessment can be a useful adjunct in our decisional armamentarium when we are called on to operate on patients under DAPT. Carefully designed and monitored randomised studies are needed to verify the validity of this approach.

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The full list of references is included in the online article at www.cardiovascmed.ch.

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